Myelosuppression and neutropenia represent the major dose-limiting toxicity of cancer chemotherapy. Chemotherapy-induced neutropenia may be accompanied by fever, presumably due to life-threatening infection, which generally requires hospitalization for evaluation and treatment with empiric broad-spectrum antibiotics. The resulting febrile neutropenia is a major cause of the morbidity, mortality, and costs associated with the treatment of patients with cancer. Furthermore, the threat of febrile neutropenia often results in chemotherapy dose reductions and delays, which can compromise long-term clinical outcomes. Prophylactic colony-stimulating factor (CSF) has been shown to reduce the incidence, severity, and duration of neutropenia and its complications. Guidelines from the American Society of Clinical Oncology recommend the use of CSF on the basis of the myelosuppressive potential of the chemotherapy regimen. The challenge in ensuring the appropriate and cost-effective use of prophylactic CSF is to determine which patients would be most likely to benefit from it. A number of patient-, disease-, and treatment-related factors are associated with an increased risk of neutropenia and its complications. A number of clinical predictive models have been developed from retrospective datasets to identify patients at greater risk for neutropenia and its complications. Early studies have demonstrated the potential of such models to guide the targeted use of CSF to those patients who are most likely to benefit from the early use of these supportive agents. Additional prospective research is needed to develop more accurate and valid risk models and to evaluate the efficacy and cost-effectiveness of model-targeted use of CSF in high-risk patients.
worry is undergoing further validation.[18] Perhaps of greatest importance, the complications of neutropenia can lead to reductions in chemotherapy dose intensity, adversely affecting long-term patient outcomes. The occurrence of neutropenia often leads physicians to reduce the chemotherapy dose or delay subsequent cycles of treatment. The net result is the delivery of lower relative dose intensity.[19-21] In potentially curable cancers, such as early-stage breast cancer and non-Hodgkin's lymphoma, there is considerable evidence that such chemotherapy dose alterations are associated with lower disease-free and overall survival.[4-6,8] The extent to which chemotherapy dose intensity was modified in major randomized clinical trials has been explored in a systematic review of the literature on chemotherapy in patients with early-stage breast cancer and non-Hodgkin's lymphoma. Data on relative dose intensity delivered were reported inconsistently and in various ways in the trials analyzed in this study, with 40% of the trials not reporting dose intensity information at all.[22] Studies of practice patterns have also shown the extent to which chemotherapy dose reductions and delays occur in practice. A survey of practice patterns in more than 20,000 patients treated with chemotherapy in the adjuvant setting for breast cancer found that 56% of patients were treated with a relative dose intensity less than 85% of the reference standard, increasing to 67% of patients aged 65 years and older.[20] Several factors may influence the relative dose intensity delivered, including both planned and unplanned dose reductions and treatment delays (Table 1). The Role of Colony-Stimulating Factor Prophylactic colony-stimulating factor (CSF) is associated with a reduced risk of febrile neutropenia, documented infection, and the need for dose reduction or treatment delay, often enabling the delivery of full dose intensity.[23-25] Clinical practice guidelines for the use of the CSF have been developed by the American Society of Clinical Oncology (ASCO).[26] These guidelines currently support the routine use of prophylactic CSF in patients treated with a chemotherapy regimen with an average risk of febrile neutropenia of 40% or greater. These guidelines were supported by early economic analyses based on a limited assessment of the direct medical costs of hospitalization for febrile neutropenia at a single institution.[27] This model found that CSF use is associated with a reduction in cost when the risk of febrile neutropenia is above the 40% threshold. The risk threshold is the breakeven point at which the added cost of the CSF is offset by the reduction in the costs of hospitalization for febrile
neutropenia. The costs of hospitaliza-
I neutropenia have been further studied both within single-institution and in multi-institution studies. Incorporating updated cost estimates into this economic model provides threshold risk estimates closer to 20% (Figure 1). The ASCO CSF guidelines are currently being revised in consideration of this and other additional clinical and economic information. Risk thresholds for the cost-saving use of CSF have been further evaluated in sensitivity analyses and are seen to depend on the assumed baseline

Figure 1: Risk Threshold—The risk threshold at which the cost of CSF is offset by the reduction in the costs of hospitalization for febrile neutropenia (FN). CSF = colony-stimulating factor. Adapted from Lyman.[28]

Figure 2: Treatment Environment and Prognostic and Predictive Factors—BSA = body surface area; CSF = colony-stimulating factor; FN = febrile neutropenia; HMO = health maintenance organization; LOS = length of stay; RDI = relative dose intensity; SN = severe neutropenia.
risk of febrile neutropenia. It is clear that some chemotherapy regimens are more likely to cause serious myelosuppression than others, but much about the patterns and incidence of chemotherapy-induced neutropenia with the regimens remains unknown. A survey of the literature for the rates of neutropenia in randomized clinical trials of chemotherapy found that the rates of myelosuppression and its complications often were not reported.[22] When they were reported, the rates of hematologic toxicity with the same and similar regimens varied greatly, making it difficult to assess the actual risk. The actual risk has been shown to vary with a large number of treatment-, disease-, and patient-related characteristics. The use of a specified risk threshold for a given regimen to select patients for first-cycle CSF use assumes an average population risk profile. There clearly is a need to "individualize" the risk by considering a specific patient's risk factors. This can be most reliably and reproducibly done by using a risk model to select patients for CSF prophylaxis. Whether to use CSF in accordance with a costminimization model with a specified risk threshold is an economic decision that is based on population risk, and it does not take into account the possible clinical benefits in individual patients in whom neutropenic complications could be avoided.[27] The optimal cost-effective use of CSF hinges on using it in those patients who are most likely to benefit from it, and being able to predict who those patients are. In the absence of reliable values for chemotherapy regimen-specific risks, clinicians often use various patient characteristics to get an idea of a patient's risk for neutropenia and its complications. The ASCO guidelines define "special circumstances" as patient populations in whom the risk is high and primary prophylaxis with CSF is recommended. These include extensive prior treatment, prior radiation therapy to considerable marrow-producing bone, and risk factors for infection, including open wounds, low performance status, and reduced immune function. However, the list of these special circumstances is not comprehensive, nor is the list routinely used in selecting patients for first-cycle CSF management. The lack of uniform standards can leave oncologists uncertain about which patients are at greatest risk for neutropenic complications. A "watch and wait" approach is often used, in which patients who experienced severe or febrile neutropenia in the first cycle are given CSF after chemotherapy in later cycles. Such "secondary prophylaxis," while reasonable in lower-risk settings, is not a desirable option in those at greater risk, given the life-threatening nature of febrile neutropenia and demonstration with several chemotherapy regimens that the greatest risk of the initial episode of febrile neutropenia occurs early in the treatment course.[29-31] Initiating CSF later in the treatment course forces most patients to experience the very complication they are intended to prevent. Clearly, a new strategy is needed to better select patients for early CSF management.

Risk Models for Neutropenia
Considerable research has been directed toward identifying patient-, disease-, and treatment-related factors associated with the risk of neutropenia and its complications. The focus has moved from the uncertainty of reported risk associated with various regimens in highly selected populations to a more focused assessment of risk in the individual patient based on his or her clinical condition and treatment history.[28] The purpose of clinical predictive models is to define the independent contributions of the various risk factors for neutropenic complications and
Risk Assessment in Oncology Clinical Practice
Published on Physicians Practice (http://www.physicianspractice.com)

Reduced dose intensity. By identifying patients at greater risk, such models can be used to target the CSFs more efficiently and cost-effectively to those most likely to benefit from such supportive care. Predictive risk models more closely reflect the situation in clinical practice, in which patients are selected for treatment on the basis of their individual prognostic and predictive factors, while basing such decisions on explicit, objective, and reproducible measures that can be systematically applied and validated[28] (Figure 2). Risk models for neutropenic events have been studied most extensively in chemosensitive, potentially curable malignancies with full-dose chemotherapy, namely early-stage breast cancer and non-Hodgkin’s lymphoma.[32-35] Those risk factors found to be statistically significant in multivariate models in two or more studies are indicated in Figure 3. Clinical prediction models evaluate relations between risk factors and clinical outcomes, such as hospitalization for febrile neutropenia or reduced chemotherapy dose intensity. Risk models can be based on pretreatment characteristics alone (unconditional) or include the initial results with treatment (conditional). Some obvious pretreatment factors are advanced age, low performance status, comorbidities, and prior treatment. Additional risk factors found to be useful in risk models in patients with non-Hodgkin’s lymphoma include serum albumin levels, lactate dehydrogenase levels, bone marrow involvement, and soluble tumor necrosis factor receptor levels.[33-35] The most common type of conditional model for predicting later neutropenic complications incorporates the patient’s early hematologic response to chemotherapy, which can identify patients at increased risk for subsequent neutropenic events who are likely to benefit from CSF support.[32,37] Conditional models are most useful with regimens that are associated with a relatively low average risk in the early cycles of treatment, while unconditional models are more useful when the early risk of neutropenic events is relatively high. An example of an unconditional risk model has recently been presented that identified five independent factors associated with an increased risk of hospitalization for febrile neutropenia: age 65 years or greater, serum albumin levels 3.5 g/dL or less, planned average reduced dose intensity 80% or more, pretreatment ANC 1.5 $10^9$/L or less, and hepatic disease.[36] This model was then used to classify patients as being at low, medium, or high risk according to how many risk factors were present.[36] Economic evaluations have shown the ability of clinical prediction models to increase cost savings and the cost-effective application of CSF by enabling targeted use in patients at greatest risk and most likely to benefit.[29,38] For instance, using a validated conditional model for identifying patients treated with adjuvant chemotherapy for early-stage breast cancer who are at increased risk for future neutropenic events that are likely to compromise dose intensity, Silber and colleagues showed that a strategy of targeting G-CSF in the 50% of patients at greatest risk was associated with an average cost-effectiveness of approximately $34,000 per life-year gained.[38] Evaluating Risk Models Most of the risk models for chemotherapy-induced neutropenia that have been developed to date have been retrospective in design, fail to provide clearly defined hypotheses, and lack important data elements for adequate analysis. Clinical predictive models should be developed from studies that minimize bias by stating the hypothesis in advance and providing clear inclusion and exclusion criteria. Any subgroup analyses that are to be performed should be stated in advance, and any differences in the outcomes between subgroups should be assessed by testing the interaction between the prognostic factor and the variable that defined the subgroups rather than by separate analyses within the subgroups. Studies should be designed to limit the potential for missing data, ideally to less than 10%. The issues of multiple comparisons should be considered when several prognostic factors or cut points are evaluated, and tests of significance should be adjusted accordingly. The pitfalls of stepwise multiple regression models, including model instability, and exaggeration of coefficient estimates (and $P$ values) should be acknowledged. The majority of the studies to date have not been independently validated in a similar but separate patient population. The issue of multiple testing or small sample sizes within subgroups must be properly addressed when apparent differences between subgroups are observed. A risk model should ideally be developed from a prospective, hypothesis-driven study in a large representative patient population. For this purpose, a prospective registry in different tumor types in a large community-based oncology setting has been created. The registry will make it possible to collect comprehensive patient data, including cycle-by-cycle information on hematologic function. The purpose of the registry is to develop a powerful risk model for neutropenia that is reliable in routine clinical practice.[22,39] Conclusions Neutropenia and its complications remain a major challenge in the management of patients with cancer treated with cytotoxic chemotherapy. Colony-stimulating factor is effective in reducing neutropenia and its complications across a broad range of disease categories and treatment regimens. The American Society of Clinical Oncology has developed clinical practice guidelines for the use of CSF that were supported by early economic models based on the average risk of febrile neutropenia with various
chemotherapy regimens. While updated cost studies support lower cost-savings risk thresholds in the average setting, current efforts have shifted the focus to treatment-, disease-, and patient-specific risk factors for neutropenia and its complications. Early studies of predictive models for identifying patients at increased risk for neutropenic complications show promise for clinical decision making and the effective targeting of CSF use toward those most likely to benefit. Such models have been shown to further reduce the cost associated with CSF support in patients treated with chemotherapy for cancer and to be cost-effective in responsive and potentially curable malignancies by enabling the delivery of full-dose-intensity therapy on time. A multi-institutional effort is currently under way to establish a large prospective registry of patients treated with cytotoxic therapy in order to develop accurate and valid risk models to guide clinicians in the optimal use of CSF.[39,40]

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